

Supplementary Material

Box 1 – Evaluating PK-PD Evidence: Analytical Approach

Evaluating PK-PD Evidence: Analytical Approach

Standard two-stage PK-PD analysis requires intense sampling from individual participants to generate individual parameter sets, which can be compared using secondary statistics. By contrast, *population-based PK-PD models* allow data from sparsely sampled individuals within a population in a manner that quantifies both fixed effects (observable properties, termed covariates, which affect drug handling, such as weight, age and underlying disease-state) and random effects (differences between observed and predicted parameter estimates that reflect all remaining sources of variability including intrinsic inter- and intra-individual PK variability, assay and data entry errors, and model misspecification).

Furthermore, population PK-PD models allow sampling from *simulated patient populations* in order to explore the predicted outcomes of alternative dosing regimens on exposures and the probability of PK-PD target attainment. Population PK-PD studies in which appropriate PK-PD targets defined, and dosing recommendations proposed based on simulation-based calculations of *target attainment* were, therefore, classified as most informative.

Studies in which PK-PD targets were not defined and/or simulation-based recommendations not made were graded as less informative, and descriptive PK studies without PD target definition were considered least informative.

With this in mind, points were assigned for analytical approach. Individual descriptive PK studies scored 1 point only. Population PK studies with no linked PD component were scored 2 points. Population PK-PD studies with target identification were scored 3 points and those with additional simulation-based dosing recommendations were scored the 4 points.

Analytical Approach

1. Population PK-PD study with target identification and simulation-based dosing recommendations (+4)
2. Population PK-PD study with target identification without simulation-based dosing recommendations (+3)
3. Population PK study with no linked PD component (+2)
4. Individual descriptive PK study (+1)

Box 2 – Evaluating PK-PD Evidence: Observation Quality

Evaluating PK-PD Evidence: Observation Quality

A major uncertainty in PK-PD studies relates to required sample sizes and observation frequency. The exploratory nature of PK-PD studies means that sample sizes are usually small. As a result, a robust analysis of clinical covariates including rationale for covariate selection based on population and drug-related factors is an important determinant of model validity. Such development and validation of PK-PD models requires experimental datasets describing dosing and observation events, as well as demographic data to enable covariate analysis. Relevant covariates may include maturation (age), size (total body weight and/or fat free mass), gender, race, genotype, hematological and biochemical parameters, disease severity and concomitant drug administration. Clinical and demographic data facilitate analysis of potentially relevant covariates that may explain PK-PD variability.

Pooling and meta-analysis of clinical PK-PD datasets allows the quantitative assessment of several studies and is increasingly used to increase the predictive value of PK-PD models. Meta-analysis of clinical trials allows the quantitative assessment of several studies in order to derive conclusions. A small number of PK-PD meta-analyses have examined pooled datasets and such methods have considerable potential to improve the validity and generalizability of PK-PD models and model-based simulations.

As such, PK-PD meta-analysis with prospective data pooling was scored 2 points while retrospective data pooling scored 1 point. Availability of clinical data to permit analysis of relevant covariates was scored 1 point.

Observation Quality

1. PK-PD meta-analysis with prospective (+2) or retrospective (+1) data pooling
2. Availability of clinical data to permit analysis of relevant covariates (+1)

Box 3 – Evaluating PK-PD Evidence: Model Appraisal and Validation

Evaluating PK-PD Evidence: Model Appraisal and Validation

Population pharmacokinetic modelling is widely used to understand how PK study participants are representative of the population as opposed to the healthy volunteers or highly selected patients in traditional pharmacokinetic studies (Sherwin 2012).

For the researcher, model validation provides insight into the modelled system and its inherent limitations which will require new approaches or additional data to overcome. For the clinician who takes the time to understand the model, it provides a sense of how comfortable they should be with the predictions made by the model, prior to applying the results to their patients. (Sherwin 2012).

Model-based simulations can be used to generate theoretical datasets for comparison with observational data, which can reveal model misspecification patterns that are not easily identified by other methods. These can be compared with existing or new data.

EMA guideline uses the term 'model evaluation' and outlines that this should demonstrate the final model is robust and a good description of the data; therefore, the objective of the analysis can be met [robust definition from EMA PK Guideline]

Model Appraisal and Validation

1. Acceptable observation-based diagnostics reported based on comparison of observations with population (+1) and individual (+1) predictions
2. Acceptable simulation-based diagnostics reported based on comparison with existing (+1) or novel (+2) data
3. Acceptable measures of robustness reported (+1)